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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/214,371	03/26/99	LANE D	4-20937/A/PC

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EXAMINER	
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ART UNIT	**PAPER NUMBER**
1635	16

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No.	Applicant(s)	
	09/214,371	LANE ET AL.	
	Examiner	Art Unit	
	Thomas G. Larson, Ph.D.	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 December 2000* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-11 and 13-26* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-11 and 13-26* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15)☐ Notice of References Cited (PTO-892)
16)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17)☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
18)☐ Interview Summary (PTO-413) Paper No(s). _____ .
19)☐ Notice of Informal Patent Application (PTO-152)
20)☐ Other:

1. The request filed on 12/22/00 for a Continued Prosecution Application (CPA) under 37 CFR 1.53(d) based on parent Application No. 09/214,371 is acceptable and a CPA has been established. An action on the CPA follows.

2. It is noted for the record that an amendment to the claims was not included with the request for a CPA filed on 12/22/00.

3. The amendments to the specification requested in the preliminary amendment filed 3/26/99 have not been entered. As set forth in the previous Office action (mailed 7/3/00) they are too numerous for the PTO to ensure that they are accurately entered and printed.

4. A substitute specification excluding the claims is required pursuant to 37 CFR 1.125(a) because the number of amendments to the specification requested in the preliminary amendment filed 3/26/99 are too numerous for the PTO to ensure that they are accurately entered and printed, as set forth in the Office action mailed 7/3/00.

A substitute specification filed under 37 CFR 1.125(a) must only contain subject matter from the original specification and any previously entered amendment under 37 CFR 1.121. If the substitute specification contains additional subject matter not of record, the substitute specification must be filed under 37 CFR

1.125(b) and must be accompanied by: 1) a statement that the substitute specification contains no new matter; and 2) a marked-up copy showing the amendments to be made via the substitute specification relative to the specification at the time the substitute specification is filed.

5. A continuing data paragraph stating that this is a U.S. national phase filing of PCT International Application No. PCT/EP97/03549, filed July 4, 1997, should be added as the first paragraph of the specification.

6. Claims 22 and 25 stand objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim for the reasons set forth in the Office action mailed 7/3/00. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form.

Claim 22 limits the DNA molecule to expressing a peptide of claim 2, however, claim 2 limits the compound of claim 1 that binds to MDM2 and inhibits the interaction of MDM2 and p53 to being a peptide. These limitations are already found in claims 18 and 21 from which claim 22 also depends.

Claim 25 recites the limitation "wherein the compound inhibits the binding of MDM2 to p53, but this limitation is already recited in claim 1 from which claim 25 depends.

7. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

8. Claim 13 stands rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101, as set forth in the Office action mailed 7/3/00.

9. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

10. Claims 14, 15, 17, and 23 stand rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention for the reasons set forth in the Office action mailed 7/3/00.

In *In re Wands* (8 USPQ 2d 1400, 1404; also see *Ex parte Forman*, 230 USPQ 546), the issue of enablement in molecular biology was considered and the factors to

be considered in a determination of "undue" experimentation were summarized. These factors include (a) the breadth of the claims; (b) the nature of the invention; (c) the state of the prior art; (d) the level of skill of those in the art; (e) the predictability of the art; (f) the amount of direction or guidance presented; (g) the presence or absence of working examples; (h) the quantity of experimentation necessary. See MPEP § 2164.01(a).

Regarding the breadth of the claims, claim 14 is broadly drawn to a pharmaceutical composition for the treatment or prevention of an unspecified disease that responds in an unspecified manner to the inhibition of the interaction of p53 and MDM2, wherein the composition comprises a peptide which is limited to comprising a particular generic consensus sequence and has the functional limitation of inhibiting the interaction of MDM2 and p53, or an unspecified derivative of said peptide. Claim 15 is broadly drawn to a method of preparing a composition for treating or preventing an unspecified disease that responds to the inhibition of the interaction of p53 with MDM2 wherein the composition comprises a peptide which is limited to comprising a particular generic consensus sequence and has the functional limitation of inhibiting the interaction of MDM2 and p53, or an unspecified derivative of said peptide. It is noted that the claim appears to lack specific method steps that would allow one to achieve the objective set forth in the preamble. For example, it is noted that such a method would generally comprises the step of adding the peptide to a pharmaceutically acceptable carrier. Claim 17 is

broadly drawn to a method of treating or preventing an unspecified disease that responds to the inhibition of the interaction of p53 with MDM2 wherein the composition comprises a peptide which is limited to comprising a particular generic consensus sequence and has the functional limitation of inhibiting the interaction of MDM2 and p53, or an unspecified derivative of said peptide.

With respect to the state of the art, the therapeutic application of peptides that affect targets external to the cell, such as a cell surface receptor (insulin and human growth hormone , as examples) is well known. However, the art appears to be silent regarding the successful therapeutic application of peptides that effect targets within the cell. In this particular case, the target of the therapeutic peptide (the p53-MDM2 complex) appears to be inside the cell membrane as well as the nuclear membrane, since p53 is known to be a DNA binding protein (see Bottger et al., document AP on the PTO-1449 submitted with the information disclosure statement filed 7/14/99, p. 754, col. 2, 2nd full ¶, for example). Therefore, the successful therapeutic application of the invention would require devising a method of delivering the peptide to the nucleus of the target cell. This would require providing the peptide in a form that is protected from degradation in the circulatory system, delivers an effective amount of the peptide to the required target cell, crosses the cell membrane, crosses the nuclear membrane, and avoids delivering the peptide to the lysosome, where it would be degraded.

The predictability of the art is poor. The outcome of experiments involving biological or physiological systems is generally regarded as unpredictable.

The skill in the art is extremely high, with the skilled artisan typically having a Ph.D., an M.D., or both a Ph.D., and an M.D., together with several years of postdoctoral training. However, in spite of this high level of skill the art remains undeveloped, as discussed above.

The specification provides limited guidance of a generalized nature regarding the formulation and delivery of pharmaceutical compounds (p. 14 last ¶, to p. 17). This guidance is cursory and does not go beyond what was already known in the art at the time the invention was made. Therefore, the artisan could not rely on the guidance to overcome obstacles to the successful therapeutic application of the invention. In particular, specific guidance is lacking on how to effectively delivery the required amount of the peptide to the target cell or tissue, and how to deliver the compound across the cytoplasmic and nuclear membranes without delivering the compound to the lysosome or another undesired compartment of the cell. Further, some of the guidance appears irrelevant to the successful therapeutic application of the invention. For example, one would not expect the guidance concerning formulations for oral administration to be useful because it is well-known that proteins and peptides are digested in the stomach before being adsorbed into the circulatory system.

There are no working examples of the invention that are reasonably expected to correlate with the successful therapeutic application of the invention. Note MPEP § 2164.02.

Regarding the amount of experimentation, due to the lack of guidance from the art and specification and the absence of working examples, the skilled artisan will be forced to engage in experimentation to develop therapeutic methods and compositions that meet the limits of the claims. The experimentation will include developing therapeutic methods and compositions that deliver the required amount of the peptide of the invention to the target cell or tissue, and deliver the compound across the cytoplasmic and nuclear membranes without delivering the compound to the lysosome or another undesired compartment of the cell. The method would also include determining what specific diseases can be treated by disrupting the interaction between MDM2 and p53, and the amount of peptide that must be effectively delivered to the target cell or tissue to treat or prevent the disease. Given the undeveloped state of the art, the breadth of the claims, and the unpredictability of the art, such experimentation would be extensive and of a trial-and-error nature. Such experimentation can not be considered routine.

Therefore, in weighing the factors to be considered in determining whether or not the practice of a claimed invention would require "undue" experimentation, as set forth in *In re Wands* (8 USPQ 2d at 1404), the weight of the analysis clearly favors a finding of "undue" experimentation for claims 14, 15, and 17. See MPEP §

2164.01(a), last ¶. Since the skilled artisan could not have practiced the claimed invention without engaging in undue experimentation, the specification fails to provide an enabling disclosure.

Claim 23 is broadly drawn to a method of treating or preventing an unspecified hyperproliferative disease comprising interfering with the interaction of human p53 and human MDM2 by an unspecified mechanism. This claim embraces the therapeutic delivery of the peptides of the invention, which would require undue experimentation for the reasons set forth in the analysis immediately above. It would also embrace the therapeutic application of gene therapy to deliver a nucleic acid expressing the peptide of the invention (see claims 21 and 22, for example), and the therapeutic application of antisense or triplex-forming (antigene) oligonucleotides (see claims 18-20, for example).

The state of the gene therapy, antisense, and antigene arts is relatively undeveloped with the successful therapeutic application of methods involving these arts being unknown at the time the invention was made. With regard to the delivery of an expressed peptide by gene therapy , Crystal teaches that obstacles such as inconsistent results, and a lack of suitable vectors have to be overcome before therapies based on gene transfer will be successful (Crystal, p. 409, section titled "What are the Obstacle to Successful Human Gene Transfer?"). The Report and Recommendations of the Panel to Assess the NIH Investment in Research on

Gene Therapy, which was released at about the time the application was originally filed, found that "...clinical efficacy has not been definitively demonstrated at this time in any gene therapy protocol..." and that "(s)ignificant problems remain in all basic aspects of gene therapy" (Report and Recommendations of the Panel to Assess the NIH Investment in Research on Gene Therapy, p. 1, items 2 and 3 under "The Panel Finds that"). The panel also emphasizes the lack of suitable vectors and further states that "an inadequate understanding of the biological interaction of these vectors with the host" (p. 1, item 3 under "The Panel Finds that"). Furthermore, the Panel found that the "(o)verselling of the results of laboratory and clinical studies ... has led to the mistaken and widespread perception that gene therapy is further developed and more successful than it actually is" (p. 2, lns. 2nd full ¶) and that the (e)xpectations of current gene therapy protocols have been oversold" (p. 13, last line).

With regard to the application of oligonucleotide therapeutics, such as antisense and antigene (triplex-forming) oligonucleotides, Stull et al. teach that the development of nucleic acid therapeutics, including ribozymes, is impeded by "several formidable obstacles...(that) require improving the ... targeting and delivering nucleic acids across cell membranes" (p. 476, col. 1, second full ¶). Stull et al. further state that "the delivery and entry of nucleic acid drugs into the target site remains a major obstacle to the successful introduction of this aspect of the molecular biology revolution into a clinical setting" (p. 478, col. 1 first full ¶).

Rojanasakul teaches that the effective use of oligonucleotide therapeutics "has been limited due to several problems.... (B)ecause of their large size and charge, these compounds are poorly taken up by cells and therefore may not reach their target site. Moreover, problems associated with cellular targeting, ... and affinity ... to the target site pose major challenges to the successful utilization of these compounds" (abstract, lns. 8-13). Note that the delivery concerns for antisense and antigene oligonucleotides are similar since both are oligonucleotides and must be delivered to the appropriate target site before they can act.

Regarding the predictability of the art, it is generally accepted that the results of experiments in biological systems are unpredictable. More specific to the invention, the prior art indicates that the gene therapy art is unpredictable. Crystal, for example, discloses that inconsistent results present a significant hurdle to the successful clinical practice of gene therapy (Crystal, p. 409, section titled "What are the Obstacle to Successful Human Gene Transfer?"). As another example, the NIH panel states that "it is not always possible to extrapolate from animal experiments to human studies" (Report and Recommendations of the Panel to Assess the NIH Investment in Research on Gene Therapy, p. 2, lns. 1-2; also p. 14, 3rd & 4th full ¶s) and that "(c)linical gene therapy studies reveal several problems and raise questions that cannot be otherwise anticipated" (p. 14, 5th full ¶). The delivery of oligonucleotide-based therapeutics *in vivo* appears to lack predictability, as evidenced by the general inability to successfully deliver

therapeutic oligonucleotides to the desired target in an organism, as taught by the Stull et al. and Rojanaskul references discussed above.

The level of skill in the art is extremely high with the typical artisan having a Ph.D., an M.D., or both a Ph.D. and an M.D., together with several years of postdoctoral training. In spite of this extremely high level of skill in the art, the art is relatively undeveloped and unpredictable, as discussed in the preceding paragraphs.

The specification provides limited guidance of a generalized nature regarding the formulation and delivery of pharmaceutical compounds (p. 14 last ¶, to p. 17). As discussed above, this guidance is cursory and does not go beyond what was already known in the art at the time the invention was made. Therefore, the artisan could not rely on the guidance to overcome obstacles to the successful therapeutic application of the invention, such as the obstacles discussed in relation to the Crystal, NIH, Stull, and Rojanasakul teachings. In particular, specific guidance is lacking on how to effectively delivery the required amount of the nucleic acid to the target cell or tissue, and how to deliver the compound across the cell membrane.

There are no working examples of the invention that are reasonably expected to correlate with the successful therapeutic application of nucleic acids for gene therapy, antisense therapy or antigene therapy. Note MPEP § 2164.02.

Regarding the amount of experimentation, due to the lack of guidance from the art and specification and the absence of working examples, the skilled artisan will be forced to engage in experimentation to develop therapeutic methods and compositions that meet the limits of the claims. The experimentation will include developing therapeutic methods and compositions that deliver the required amount of the gene or oligonucleotide of the invention to the target cell or tissue. The required experimentation would also include determining what specific diseases can be treated by disrupting the interaction between MDM2 and p53, and the amount of peptide that must be effectively delivered to the target cell or tissue to treat or prevent the disease. Given the undeveloped state of the therapeutic nucleic acid art, the breadth of the claims, and the unpredictability of the art, such experimentation would be extensive and of a trial-and-error nature. Such experimentation can not be considered routine.

Therefore, in weighing the factors to be considered in determining whether or not the practice of a claimed invention would require "undue" experimentation, as set forth in *In re Wands* (8 USPQ 2d at 1404), the weight of the analysis clearly favors a finding of "undue" experimentation for claim 23. See MPEP § 2164.01(a), last ¶. Since the skilled artisan could not have practiced the claimed invention without engaging in undue experimentation, the specification fails to provide an enabling disclosure.

11. Claims 18-22 stand rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for inhibiting the interaction between MDM2 and p53 *in vitro*, does not reasonably provide enablement for inhibiting the interaction *in vivo*. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims for the reasons set forth in the Office action mailed 7/3/00..

The following determination of undue experimentation for the *in vivo* portion of the scope of claims 18-23 was made following the analysis set forth in *In re Wands* (8 USPQ 2d 1400, 1404; also see *Ex parte Forman*, 230 USPQ 546), as set forth above.

Claim 18 broadly embraces a method comprising the step of inhibiting the interaction of p53 and MDM2 both the *in vivo* and *in vitro* by an unspecified means. The *in vivo* portion of this claim clearly reads on the therapeutic application of the method as the disclosed utility for inhibiting the interaction between p53 and MDM2 appears to be for therapeutics purposes. The method of claim 18 embraces the inhibition of MDM2 using either antisense or antigene (triplex-forming) oligonucleotides, as set forth in dependent claims 19 and 20. These claims limit claim 18 to the inhibition of binding being due to reduction in MDM2 expression mediated by the administration of an unspecified antisense oligonucleotide or an unspecified antigene oligonucleotide to the target cell. The method of claim 18

further embraces the expression of a peptide through gene therapy methods, as evidenced by claims 21 and 22. However, the therapeutic application of nucleic acids, whether it be for the expression of an inhibitory peptide, or the antisense- or antigene-mediated inhibition of gene expression, is not enabled for the reasons set forth above in the rejection of claim 23 for lack of enablement.

12. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

13. Claims 1, 3, 6-8, 10, 11, 14-17, and 24 stand rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention for the reasons set forth in the previous Office action.

Each of claims 1, 10, 11, 16, 17, and 24 recites the limitation "... capable of binding ...". Since "capable of denotes a latent property, the use of this language makes it unclear whether or not the recited limitation is intended to form part of the claimed subject matter, rendering the claim indefinite. It is suggested that the claims recite "which binds".

Each of the claims 3, 7, 8, 10, 11, 14, , 15, and 17 recites specific amino acids in the alternative, with the additional limitation that a particular amino acid is preferable. The use of the language "preferably" leaves the claim indefinite because

it is unclear exactly what is being claimed. It is unclear whether the claim is limited to embracing the preferred amino acid or to embracing all of the amino acids of each group.

Claim 6 recites " ... the peptide according to claim 3 wherein the peptide is a fragment comprising at least 8 consecutive amino acids...." However, since the peptide shown in formula (I) in claim 3 must have at least 10 amino acids, an 8 amino acid peptide would no longer be the peptide of claim 3. Claims 7 and 8 are indefinite for the same reasons.

Claim 13 provides for the use of the compound of claim 1, but, since the claim does not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. Claim 13 is indefinite because it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

Claim 15 provides for the use of the peptide of the invention, but, since the claim does not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. Claim 15 is indefinite because it merely recites a use without any active, positive steps delimiting how this use is actually practiced. For example, a method of using a compound to prepare a pharmaceutical composition generally requires at least the step of combining the compound with a pharmaceutically acceptable carrier.

Claim 11 is indefinite for reciting a broad range or limitation together with a narrow range or limitation. A broad range or limitation together with a narrow range or limitation that falls within the broad range or limitation (in the same claim) is considered indefinite, since the resulting claim does not clearly set forth the metes and bounds of the patent protection desired. Note the explanation given by the Board of Patent Appeals and Interferences in *Ex parte Wu*, 10 USPQ2d 2031, 2033 (Bd. Pat. App. & Inter. 1989), as to where broad language is followed by "such as" and then narrow language. The Board stated that this can render a claim indefinite by raising a question or doubt as to whether the feature introduced by such language is (a) merely exemplary of the remainder of the claim, and therefore not required, or (b) a required feature of the claims. Note also, for example, the decisions of *Ex parte Steigewald*, 131 USPQ 74 (Bd. App. 1961); *Ex parte Hall*, 83 USPQ 38 (Bd. App. 1948); and *Ex parte Hasche*, 86 USPQ 481 (Bd. App. 1949). In the present instance, claim 11 recites the broad recitation "to purify a binding partner," and the claim also recites "particularly MDM2" which is the narrower statement of the range/limitation.

Claim 22 is indefinite because it depends from both claim 21 and claim 2, leaving unclear from which claim it is intended to depend.

14. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

15. Claims 1, 2, 18-22 and 24-26 stand rejected under 35 U.S.C. 102(e) as being anticipated by Burrell et al. (US Patent No. 5,420,263) for the reasons set forth in the Office action mailed 7/3/00.

Claims 1, 2, and 24-26 are drawn to a peptide that binds to MDM2 and inhibits the binding of MDM2 to p53. Claim 18 is drawn to a method of inducing apoptosis or growth arrest in tumor cells *in vitro* comprising the step of inhibiting the interaction of MDM2 and p53. Claims 19 and 20 respectively limit the method of claim 18 to the interaction being blocked by the administration of an antisense or triplex-forming oligonucleotide. Claims 21 and 22 respectively limit the method of claim 18 to the interaction being inhibited by the administration of a DNA molecule that expresses a peptide that interferes with the interaction of MDM2 and p53.

Burrell et al. teach methods and compounds for inhibiting the interaction of MDM2 and p53. These include the use of MDM2 inhibiting antisense or triplex-forming nucleic acids (col. 6, lns. 44-52), antibodies specific for the portions of MDM2 or p53 required for MDM2-p53 binding (col. 6, lns. 58-64), and a p53-derived peptide that binds to the p53-binding site on MDM2 (col. 7, lns. 9-37). Burrell et al. teach the administration to a cell of a DNA construct expressing the portion of p53

that interacts with MDM2 as a means for inhibiting p53-MDM2 interaction (col. 7, lns. 26-37). Although the preamble of claim 18 states that the method is applied to cells containing wild-type p53 and non-elevated levels of MDM2, the preamble is considered non-limiting because the method does not depend on it for completeness since the method step of inhibiting the interaction between p53 and MDM2 *in vitro* can stand on its own, in a method of inhibiting the interaction of p53 and MDM2, for example (note MPEP § 211.02).

16. Claims 1-8, 10, 11, 18, 21, 22 and 24-26 stand rejected under 35 U.S.C. 102(e) as being anticipated by Picksley et al. (either one of US Patent Nos. 5,702,908 and 5,770,377, were '377 is a continuation in part of '908) for the reasons set forth in the Office action mailed 7/3/00. It is noted that WO 96/02642, which is cited in the information disclosure filed 7/14/99 (document AH) and in the search report for PCT international application PCT/EP97/03549 (of which this application is a US National Phase filing), claims priority to the US applications from which the '908 and '377 patents issued.

Claims 1, 2, and 24-26 are drawn to a peptide binds to MDM2 and inhibits the binding of MDM2 to p53. Claims 3-4 limit the compound of claim 2 to having formula (I), or a derivative thereof, and being not more than 15 amino acids in length. Claim 5 recites a group of peptides that includes a derivative of a peptide having the sequences Q-P-T-F-S-D-Y-W-K-L-L-P (Seq. Id. No: 6) and P-X-F-X-D-Y-

W-X-X-L (Seq. Id. No: 7). Claims 6 to 8 limit the compound of claim 3 to having or comprising an eight or nine amino acid consensus sequence (formulae (Ib) and (1c)). Claim 10 is drawn to a method of inhibiting the binding of p53 to MDM2 comprising the step of obtaining a peptide comprising formula (I) and inhibiting the binding of p53 to MDM2. Claim 11 is drawn to a method of using a peptide or derivative of formula (I) to purify a binding partner comprising obtaining a peptide comprising formula (I) and using the peptide to purify a binding partner. Claim 18 is drawn to a method of inducing apoptosis or growth arrest in tumors comprising the step of inhibiting the interaction of MDM2 and p53. Claims 21 and 22 respectively limit the method of claim 18 to the interaction being inhibited by the administration of a DNA molecule that expresses a peptide that interferes with the interaction of MDM2 and p53.

Picksley et al. teach fragments of human p53 that bind to human MDM2 to inhibit binding of p53 to MDM2 and that can be used to identify binding partners (Example 3, beginning col. 9, ln.65, in '908). Picksley et al teach particular peptide sequences of 6, 7, 10, and 15 residues (respectively SEQ. ID. NOS: 2, 26, 27, 1 and 6 from '908), and teaches that the peptide may be up to 28 residues (col. 2, lns. 55-63, in '908) with six to 10 amino acids being preferred (col. 2, lns. 63-66, in '908). These sequences comprise the consensus sequences of formulae (I), (Ib), or (Ic), with the exception that R_3 is the amino acid leucine (L), which is interpreted to be a derivative of the peptide of the formula set forth in the claims for the purposes of

this analysis. Note that the specification specifically defines a derivative as encompassing "more preferably one or two amino acids in the motif of formula (I) are replaced with another ... natural amino acid" (pp. 4, bridging ¶, especially lns. 7-9). In the sequences of claim 5, P is substituted by E, and Y is substituted by L in the "derivative" sequences disclosed by Picksley et al. Picksley et al. further disclose a method of inhibiting the binding of MDM2 to p53 using the disclosed fragments and inhibiting the growth of tumor cells using the fragments to inhibit the binding of MDM2 to p53 (col. 4, lns. 1-13). Picksley teaches that such compounds may be delivered to the cells by providing a DNA which encodes and expresses the desired peptide (col. 4, lns. 38-54). Although the preamble of claim 18 states that the method is applied to cells containing wild-type p53 and non-elevated levels of MDM2, the preamble is considered non-limiting because the method does not depend on it for completeness since the method step of inhibiting the interaction between p53 and MDM2 *in vitro* can stand on its own, in a method of inhibiting the interaction of p53 and MDM2, for example (note MPEP § 211.02).

17. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

18. Claim 16 stands rejected under 35 U.S.C. 103(a) as being unpatentable over Picksley et al. (US Patent No. 5,702,908) in view of what is well known in the prior art for the reasons set forth in the Office action mailed 7/3/00.

The claim is drawn to a method of making a peptide a peptide that binds to MDM2 and inhibits the binding of MDM2 to p53, which method essentially comprises the step of reacting a fragment of the peptide having a free or derivatized carboxy group with a second fragment of the peptide having a an amino or derivatized amino group under conditions to form an amide bond.

Picksley et al. teach fragments of human p53 that bind to human MDM2 to inhibit binding of p53 to MDM2 (col. 2, lns. 40-54 for example). Picksley teaches preparing the peptide fragments using recombinant DNA techniques (col. 7, ln. 55, col. 8, ln. 12), and does not teach preparing the peptide by chemical synthesis.

The chemical synthesis of peptides by reacting a fragment of the peptide having a free or derivatized carboxy group with a second fragment of the peptide having a an amino or derivatized amino group under conditions to form an amide bond are well known in the art, as evidenced by the specification at p. 10, ln. 6, to p. 13, ln. 15.

It would have been obvious the artisan of ordinary skill to synthesize the peptides taught by Picksley et al. using methods well known in the art at the time the invention was made. One would have been motivated to provide an alternative

to the recombinant method of preparing peptides because it would avoid the necessity of preparing the necessary coding constructs and vectors, eliminate the requirement of isolating and validating the host cells transformed with the desired recombinant construct, and the eliminate the difficulties associated with purifying the desired peptides form the complex mixture of proteins and peptides produced by the host cells used to express the peptide. One would have had a reasonable expectation of success because the methodology for the chemical preparation of peptides is routine in the art (see specification p. 13, lns. 5-13 for example).

19. No claim is allowed.

20. This is a Continued Prosecution Application (CPA) of applicant's earlier Application No. 09/214,371. All claims are drawn to the same invention claimed in the earlier application and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the earlier application. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action in this case. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory

period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no, however, event will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

21. Certain papers related to this application may be submitted to Art Unit 1635 by facsimile transmission. The FAX numbers are (703) 308-4242 and (703) 308-3014. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 CFR 1.6(d)). NOTE: If applicant does submit a paper by FAX, the original copy should be retained by the applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED, so as to avoid the processing of duplicate papers in the Office.

Unofficial papers, such as draft responses, may be transmitted to the examiner directly at (703) 305-7939. It is recommended that the examiner be notified when a fax is sent to this number.

Any inquiry concerning this communication or earlier communications should be directed to Thom Larson, whose telephone number is (703) 308-7309. The examiner normally can be reached Monday through Friday from 9:00 AM to 5:30 PM, EST. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. George Elliott, can be reached at (703) 308-4003.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group Receptionist, whose telephone number is (703) 308-0196.

Thomas G. Larson, Ph.D.
Examiner

ROBERT A. SCHWARTZMAN
PRIMARY EXAMINER